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UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

ASTRAZENECA AB, AKTIEBOLAGET HÄSSLE, ASTRAZENECA LP, KBI INC., and KBI-E INC., Plaintiffs and Counterclaim Defendants, v. HANMI USA, INC., HANMI PHARMACEUTICAL CO., LTD., HANMI FINE CHEMICAL CO., LTD, and HANMI HOLDINGS CO., LTD., Defendants and Counterclaim Plaintiffs.	Civil Action No. 3:11-CV-00760-JAP-TJB

SUPPLEMENTAL DECLARATION OF JERRY L. ATWOOD, Ph.D.

I, Jerry L. Atwood, state and declare as follows:

1. I make this declaration in further support of my Declaration of November 3, 2011, which was prepared in conjunction with Hanmi's initial *Markman* submission in the above-captioned matter. I incorporate herein the substance of my previous Declaration, including my background, the scope of my review, and the credentials of a person of ordinary skill in the art.

2. Further to the materials I have relied upon previously, I have considered the November 7, 2011 Declaration of Stephen G. Davies (D.I. 133-3) and exhibits attached thereto, prepared in conjunction with AstraZeneca's Initial *Markman* Brief. I have also considered Dr. Davies' Declaration, deposition transcript and related exhibits, as well as the additional materials referred to in this declaration.

A. Issues Regarding "Salt" Scope In Both Patents

"alkaline salt" -- '504 patent

3. Each of claims 1, 6 and 7 of the '504 patent calls for an "alkaline salt" of (-)-omeprazole. For the reasons set forth in my previous Declaration, those salts are "Na^+, Mg^{2+}, Li^+, K^+, Ca^{2+} or $N^+(R)_4$ salt" where R is an alkyl with 1-4 carbon atoms. In addition, I understand that AstraZeneca has now asserted claims 3, 5, and 10 in this litigation.

4. Claim 3 recites the pharmaceutical formulation of claim 1, wherein the alkaline salt is a Na^+, Mg^{2+}, Li^+, K^+, Ca^{2+} or $N^+(R)_4$ salt. Claim 5 recites the pharmaceutical formulation of claim 1, wherein the alkaline salt is a sodium or magnesium salt. Claim 10 recites the method of claim 6 or 7 wherein the alkaline salt is a Na^+, Mg^{2+}, Li^+, K^+, Ca^{2+} or $N^+(R)_4$ salt.

5. Dr. Davies has stated that the term "alkaline salt" means any basic salt that is suitable for use in a pharmaceutical formulation. I disagree that the "alkaline salt" as claimed in the '504 patent can include any basic salt and that the patent requires that the salt be suitable for use in a pharmaceutical formulation.

Any Basic Salt

6. Dr. Davies defines "alkaline salts" of the claims as "any basic salt" and includes within his definition all of the Group I and Group II metals, as well as the ammonium salt, NH_4^+ and others. (Davies Decl. ¶ 36; Davies Tr. 149-151 (Ex. 1).) His Declaration states:

> a person of ordinary skill would understand that suitable cations for "alkaline salts" include, at least, cations of all of the metals in Groups I and II (lithium, sodium, potassium, rubidium, caesium, beryllium, magnesium, calcium, strontium or barium) as well as ammonium, which is often considered an honorary alkaline salt because ammonia, when dissolved in water, affords a basic solution. (Davies Decl. ¶ 36.)

7. In support, Dr. Davies cites the Chambers Dictionary of Science and Technology, which defines "alkali metals" to mean "lithium, sodium, potassium, rubidium, and caesium, all monovalent metals in the first group of the periodic system;" and defines "alkaline earth metals" to mean "beryllium, magnesium, calcium, strontium, barium, and radium, all divalent metals in the second group of the periodic system." (Davies Decl., p. 11 at n. 1.)

8. Broadly, Dr. Davies explained that *all alkaline salts* would be included within his definition (Davies Tr. 161-162; 172), which number in the hundreds of thousands or even millions (Davies Tr. 147-148).

9. For example, in addition to the $N^+(R)_4$ salts described in the specification (where R is an alkyl group with 1-4 carbon atoms), Dr. Davies also includes within his definition of "alkaline salts" $N^+(R)_4$ salts, where R is an alkyl group having *more* than 1-4 carbon atoms, *e.g.*, 5, 6, 7 or greater. (Davies Tr. 157.)

10. Dr. Davies also includes within his definition of "alkaline salts" certain amines such as pentamethyl guanidine salts and guanidinium salts, but excludes other amines such as

pyridine or piperadine salts. (Davies Tr. 158-159; 170-171.) He excludes amino acids salts from his definition of "alkaline salts." *Id.*

11. Dr. Davies further includes within his definition of "alkaline salts" *all metals* and he stated *that there are a lot of metals.* (Davies Tr. 160.)

12. For the reasons stated in my initial declaration, the term "alkaline salts" is properly defined as the five inorganic species and the one organic genus described in the '504 patent specification, and I disagree that the intrinsic record of the '504 patent supports the broad, sweeping definition of "alkaline salt" advanced by Dr. Davies.[1] There is no disclosure in the '504 patent suggesting that the alkaline salts of the claimed pharmaceutical formulations could possibly include all metal salts, all Group I and Group II elements salts, ammonium and all tetraalkyl ammonium salts, pentamethyl guanidine salts and guanidinium salts, or any basic salt. There is no disclosure in the '504 patent of how to make or use the universe of basic salts described by Dr. Davies. The structure and properties of the hundreds of thousands of salts are so widely varied that no person skilled in the art would view the disclosure of the six recited species as representative of all alkaline salts as defined by Dr. Davies. To the contrary, persons skilled in the art would know that many of the salt species included with Dr. Davies' definition are neither disclosed in the '504 patent, "suitable for use in pharmaceutical formulations," nor is any method provided for making them.

13. For example, Dr. Davies states clearly that rubidium, cesium, beryllium, and barium would be understood as included within the definition of "alkaline salt." (Davies Decl. ¶ 36.)

[1] The '504 patent states that "the present invention refers to the new Na^+, Mg^{2+}, Li^+, K^+, Ca^{2+} or $N^+(R)_4$ salts of the single enantiomers of omeprazole." (Col. 2, ll. 42-49). Dr. Davies testified he did not specifically consider this teaching of the '504 patent in formulating his definition of "alkaline salts." (Davies Tr. 155-156.)

14. Beryllium is highly toxic, especially by inhalation, and reported as a known carcinogen by OSHA.[2] Beryllium intoxication has been reported to cause pneumonitis and osteosarcoma in animals as well as bone tumors in humans.[3] Other authors confirm the extreme toxicity of beryllium:

> Beryllium causes chronic beryllium disease (CBD), which is a fatal disease of the 20th century and has been confirmed in eight cases by lung biopsy and the blood beryllium lymphocyte proliferation test (Be LPT). It also causes a number of diseases such as bronchitis, pulmonary granulomatosis and hepatomegaly, because the liver is the target organ of beryllium. Its accumulation causes cellular death. Beryllium also interacts with DNA and causes gene mutation, chromosomal aberration and sister chromatid exchange in cultured somatic cells. [footnotes omitted].[4]

15. No one skilled in the art would expect beryllium to be an "alkaline salt" of the '504 patent claims.

16. Cesium is a Group I element that has certain chemical properties similar to potassium, sodium, and lithium. Dalal, et al., report that cesium chloride has antineoplastic properties, but that patients taking cesium chloride as an anticancer compound acquired QT prolongation and sustained monomorphic ventricular tachycardia.[5] Yung also reports that cesium is a carcinogen, and that an excess of cesium can cause neuromuscular toxicity and convulsions.[6]

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[2] GESSNER G. HAWLEY, THE CONDENSED CHEMICAL DICTIONARY (Van Nostrand Reinhold Co.) (10th ed. 1981). (Ex. 3.)

[3] Christoph Y. Yung, *A Synopsis on Metals in Medicine and Psychiatry*, 21:1 PHARMACOLOGY BIOCHEMISTRY & BEHAV. 41-47 (1984). (Ex. 4.)

[4] Pragya Sharma et al., *Beryllium-induced Toxicity and its Prevention by Treatment with Chelating Agents*, 20 J. APPLIED TOXICOLOGY 313-18 (2000). (Ex. 5.)

[5] Anuj K. Dalal et al., *Acquired Long QT Syndrome and Monomorphic Ventricular Tachycardia After Alternative Treatment With Cesium Chloride for Brain Cancer*, 79:8 MAYO CLINIC PROC. 1065-69 (2004). (Ex. 7.)

[6] *See* Yung, discussed above in footnote 3.

17. Even though beryllium and cesium are Group I and II metals[7] and within Dr. Davies' definition of alkaline salts in the context of the '504 patent claims, a person of ordinary skill would not view either element as a suitable alkaline salt of the '504 patent due to their high toxicities.

18. Francium is a Group I element that exists only as radioactive isotopes and although it was not mentioned specifically in his Declaration, it is within Dr. Davies' definition of "at least, cations of all the metals in Groups I and II . . . ." Francium 223 is the longest lived of the isotopes, and has a half-life of 21 min. Francium is the heaviest of the alkali metal family.[8] Based on its short half-life and radioactivity, a person skilled in the art would not view francium as a suitable alkaline salt of the '504 patent.

19. Radium is another radioactive element of Group II and is within the scope of Dr. Davies' definition. (Davies Decl. ¶36 and note 1.) Radium is defined as highly toxic and emits ionizing radiation. It is destructive to living tissue and used in industrial radiography. Persons of skill in the art would not view radium as a suitable alkaline salt of the '504 patent.[9]

20. Rubidium is also a Group I element. Yung reports that an excess of rubidium can cause tetany, convulsion, and death.[10]

21. Barium is a Group II element that is used medically in preparations as a radio contrast medium. Its toxic effects are reported as including gastrointestinal symptoms, convulsions, hypertension, and cardiac arrest.[11]

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[7] A copy of the Periodic Table of Elements is provided as Ex. 13.

[8] GESSNER G. HAWLEY, THE CONDENSED CHEMICAL DICTIONARY (Van Nostrand Reinhold Co.) (10th ed. 1981). (Ex. 3.)

[9] *Id.*

[10] *See* Yung, discussed above in footnote 3.

[11] *Id.*

22. Due to the toxicities of these compounds, persons of skill in the art would not view rubidium or barium as suitable alkaline salts of the '504 patent.

23. Indeed, if the group of alkaline salts includes all metals as Dr. Davies testified (Davies Tr. 160), he has swept in numerous toxic metals from across the periodic table. Persons of ordinary skill in the art would understand that most metals referred to by Dr. Davies are toxic at a level required to achieve a pharmaceutical effect of (-)-omeprazole. For example, administration of a lead salt to humans would have disastrous consequences.

24. In addition to the toxicity and unsuitability of many of the alkaline salts included within Dr. Davies' definition, a person of ordinary skill in the art would not know if many of the other undisclosed salts included within his definition could even be prepared, or how to do so.

25. The '504 patent provides two different procedures of how to make inorganic salts and does not inform one skilled in the art how or why to select one procedure over another. Specifically, the patent generally discloses the preparation of the sodium, lithium and potassium salts of (-)-omeprazole according to one general procedure (Col. 4, ll. 51-61 (D.I. 86-2)), and preparation of the magnesium and calcium salts of (-)-omeprazole from a different procedure -- *starting with the sodium salt* of (-)-omeprazole (Col. 4, ll. 63- Col. 5, l. 6).

26. The '504 patent fails to explain why some salts of (-)-omeprazole are prepared using a metal salt hydroxide and the free base of (-)-omeprazole and other salts are only prepared from the sodium salt previously made according to this first general procedure. The '504 patent does not direct those skilled in the art which procedure should be used to prepare other, undisclosed salt species.

27. Further, the '504 patent makes clear that the process of the working Examples results in the conversion of one enantiomer to the other (+ to - and - to +) during preparation of the

sodium salts of (-)-omeprazole from the neutral form, and as well for the preparation of the magnesium salt from the sodium salt. (Col. 6, ll. 29-35.) Preparation of the (+)-omeprazole salts thus requires (-)-omeprazole or its salts as a starting point, and vice versa. The disclosure is specific as to preparation of the magnesium and sodium salts only, and there is no way to know whether chiral inversion would occur with any other alkaline salt.

28. As a result, persons skilled in the art would be unable to determine which procedure to use in preparing future alkaline salts of (-)-omeprazole (undisclosed in the '504 patent), and whether chiral inversion would necessitate selection of the opposite enantiomer as a starting material. In my view, the '504 patent disclosure of the preparation of only two species does not demonstrate that all of the possible genus members could be made in a similar way.

29. In defining "alkaline salts" as including salts such as pentamethyl guanidine salts and guanidinium salts, but excluding other amines such as pyridine or piperadine salts, as well as amino acids (Davies Tr. 158-159; 170-171), Dr. Davies explained that not all organic cationic species form alkaline salts with (-)-omeprazole, but rather, only those organic compounds that form strong bases. *Id*. There is no disclosure in the '504 patent of alkaline salts of (-)-omeprazole that are selected based on their strengths as bases. Nothing in the patent or prosecution history supports Dr. Davies' view that only strong bases would be appropriate for the formation of alkaline salts of (-)-omeprazole. Nor does Dr. Davies provide any criteria for determining the basic strength of an organic compound sufficient for persons of ordinary skill in the art to know whether that compound would be an "alkaline salt" of (-)-omeprazole as claimed.

30. As a further example, there is no explanation in the '504 patent as to how to prepare any of the ammonium salts that are described in the patent ($N^+(R)_4$), and a person of skill in the

art would not know whether ammonium salts could be prepared from the same methods as were used to prepare the inorganic salts of Examples 1-7, or would require different methods. At his deposition, I see that Dr. Davies expressed doubt as to whether or not an ammonium salt of (-)-omeprazole could even be formed.[12] (Davies Tr. 151-153.) Dr. Davies suspects that a tetrabutyl ammonium salt of (-)-omeprazole could be formed, but he doesn't know whether it would be a solid salt. (Davies Tr. 153-154.) On these points, I agree with Dr. Davies, because there is simply not enough information in the '504 patent for a person of ordinary skill in the art to know how, *or whether*, ammonium salts of (-)-omeprazole could even be formed.

31. Dr. Davies stated in an earlier declaration relating to (-)-omeprazole, that salt formation "may be a possibility for some compounds or mixtures, but would not be possible for many others." He added that a skilled person would have no means of knowing whether it would or would not work. He concluded that salt formation "would not be the first [method] contemplated by a skilled person, because the skilled person would have no expectation that 1) a salt of the enantiomer of omeprazole could be formed." (Davies Tr. at 176-178; Davies Dep. Ex. 10, p. 25, HAN0043425 (Ex. 6).) These prior statements in earlier declarations are inconsistent with Dr. Davies present statements that virtually any basic salt could be made and would satisfy the definition of "alkaline salt" in the '504 patent claims.

32. I agree with these earlier statements of Dr. Davies. Because persons of ordinary skill in the art "would have no expectation that 1) a salt of the enantiomer of (-)- omeprazole could be formed," they certainly would not be able to prepare all of the undisclosed alkaline salts of (-)-omeprazole Dr. Davies now urges are included within the scope of the claims.

[12] Dr. Davies appears to take the unusual position that if a particular alkaline salt can be formed, then it is within the scope of his definition. If it cannot be formed, then it appears to be excluded. (Davies Tr. 152.) I do not believe this is a proper methodology for determining the scope of the claims.

Suitable for use in a pharmaceutical formulation

33. Based only on the language of the claims, Dr. Davies construes that the "alkaline salts" are those "suitable for use in a pharmaceutical formulation." (Davies Decl. ¶41.) However, during his deposition, he plainly conceded that one of ordinary skill in the art would need to perform experimentation to determine if his vast field of potential salts would – in fact – be pharmaceutically acceptable. (Davies Tr. at 173-174.) This entire concept of having to test potential salts is far afield from any aspect of the intrinsic record. There is nothing about the type of testing, the methodology, the standards used to determine alleged suitability, etc. in the '504 patent. AstraZeneca and Dr. Davies graft entire new concepts requiring nebulous testing in order to determine the scope of the claims. This practice simply does not comport with the manner in which a person of ordinary skill in the art determines claim scope.

34. Nothing in the claims of the '504 patent, specification, or prosecution history requires that the alkaline salt independently be suitable for use in a pharmaceutical formulation. For example, claim 1 recites "a pharmaceutical formulation" and a "pharmaceutically acceptable carrier." The term "alkaline salt" is not modified by the terms "pharmaceutical" or "pharmaceutically acceptable." Thus, when the '504 patentees wanted to claim a formulation or a component of a formulation as "pharmaceutically acceptable," they certainly knew how to do so. That they chose not to describe the alkaline salt of claim 1 as such, informs that the correct construction of "alkaline salt" does not require the pharmaceutical limitation as suggested by Dr. Davies.

35. Moreover, in terms of determining "suitability" according to Dr. Davies' theoretical test protocol, no disclosure exists in the '504 patent that describes how "suitability" is

measured, or which tests are used, or which standards are used. Adding this type of requirement to the meaning of "alkaline salt" would inject multiple layers of ambiguity.

36. Similarly, nowhere in the patent specification or prosecution history is it defined or required that the alkaline salt *independently* be suitable for use in a pharmaceutical formulation. For example, the patent specification refers to pharmaceutically acceptable carriers, pharmaceutically acceptable enteric coating materials, and pharmaceutically acceptable solvents. These descriptions show that the '504 patentees knew how to describe individual components of a formulation as pharmaceutically acceptable. That they chose to require other components of the formulation to be "suitable for use in a pharmaceutical formulation," -- *but not alkaline salts* -- demonstrates that the term "alkaline salt" is not so limited.

37. While the carrier must be pharmaceutically acceptable, and the overall formulation is a pharmaceutical one, nothing in the intrinsic evidence of the '504 patent requires that the "alkaline salt" be independently suitable for pharmaceutical administration.

38. Contrary to Dr. Davies' opinion, it does not necessarily follow that a pharmaceutical formulation of claim 1 necessarily requires that the alkaline salt also be independently suitable for use in a pharmaceutical formulation. In some cases alkaline salts of pharmaceutical compounds can be otherwise *unsuitable*, but the formulation as a whole -- including the active pharmaceutical ingredient and all other components – can be made to be pharmaceutically acceptable.

39. For example, potassium salts have been considered unsuitable for oral formulations such as suspensions and syrups because of their bitter taste. However, when taste masked with

sweeteners or other agents, the potassium salt of an active pharmaceutical ingredient can be made suitable for pharmaceutical administration.[13]

40. In another example, a poorly water-soluble alkaline salt of a pharmaceutical compound can be made to be suitable for use as a pharmaceutical formulation by increasing its water solubility through formulation techniques. Nimesulide is a potent nonsteroidal anti-inflammatory drug successfully used for the treatment of different inflammatory conditions and rheumatoid arthritis. U.S. Pat. No 5,744,165 (Nimesulide Salt Cyclodextrin Inclusion Complexes) (Ex. 8) reports that nimesulide is practically insoluble in water (Col. 1, ll. 51-55), and while the alkaline and alkaline earth salts of nimesulide were more water-soluble, the patent states that "due to the high pH value of their solutions, the nimesulide alkali and alkaline earth salts were not practical for use as pharmaceuticals" (Col. 1, ll. 39-41). To remedy these problems, the '165 patent is directed to increasing the water solubility of alkaline salts of nimesulide by forming inclusion complexes with cyclodextrins. By formulating differently, patentees were able to transform unsuitable alkali/alkaline earth metal salts of nimesulfide into those suitable for use in pharmaceutical formulations .

41. These examples confirm the understanding of a person of ordinary skill in the art, that an alkaline salt -- otherwise unsuitable for use in a pharmaceutical formulation for any one of a variety of reasons -- can be made to be suitable by formulation, modification and other techniques. For these reasons, I disagree that the term "alkaline salt" in the '504 patent includes any limitation directed to pharmaceutical acceptability.

42. In an earlier litigation against DRL, I understand that Astra Zeneca proposed a construction of "alkaline salt" that is different than the construction it proposes in the present

[13] *See* Berge (1977) describing potassium salts as exhibiting "inferior palatability." D.I. 112-4 at 9 (left col.) and other taste-masking examples discussed at pp. 4, 8.

case. Specifically, I understand AstraZeneca did not previously propose that the term "alkaline salt" as used in the claims of the '504 patent contained a limitation that they be "suitable for use in a pharmaceutical formulation," and of course, they do so presently. Dr. Davies explained at his deposition that – in the previous DRL case – he was defining alkaline salt, whereas in the present case, he is defining an alkaline salt in the context of claim 1. (Davies Tr. 80-81.) That distinction is unclear and nonsensical to me because in both cases the term "alkaline salt" at issue was and is in claim 1 of the '504 patent asserted by AstraZeneca.

"pharmaceutically acceptable salt" – '192 patent

43. The '192 patent specification makes clear that the term "pharmaceutically acceptable salt" refers to both acid and alkaline pharmaceutically acceptable non-toxic salts. ('192 patent, col. 4, ll. 13-16.) As I stated in my previous Declaration, that definition would be considered dominant and controlling by a person of ordinary skill in the art.

44. Notwithstanding this express definition, Dr. Davies urges that the "acid" salts of this definition do not apply to (-)-omeprazole as the active pharmaceutical ingredient, but rather, apply only to the other therapeutic ingredients referred to in this paragraph. (Davies Decl. ¶¶ 65, 66.) I disagree with Prof. Davies' interpretation.

45. Preceding the express definition of "pharmaceutically acceptable salt" is a sentence that states:

> The pharmaceutical compositions of the present invention comprise the (-)-enantiomer of omeprazole as active ingredient, or a pharmaceutically acceptable salt *thereof*, and may also contain a pharmaceutically acceptable carrier and optionally, other therapeutic ingredients.

46. There is little question but that the pharmaceutically acceptable salt *thereof* refers to the (-)-enantiomer of omeprazole, and nothing else in that sentence -- either the

pharmaceutically acceptable carrier or the other therapeutic ingredients. Dr. Davies' strained reading of this passage is simply unsound and would be at odds with how one of ordinary skill in the art would interpret this plain passage.

47. For example, he posits that the "other therapeutic agents" need not be limited to alkaline salts, and may be employed as acid addition salts. (Davies Decl. ¶ 66.) There is no support for this explanation, for at least the following reasons:

- there are no "other therapeutic agents" disclosed anywhere in the '192 patent and so there is no basis to conclude that salts of those agents could even be formed,
- nor is there any way to conclude that the "other therapeutic agents" can form acid salts in particular, in a way that supports Dr. Davies hypothesis, and
- "pharmaceutically acceptable salt" is only used in connection with(-)-omeprazole, and never in conjunction with other therapeutic agents.

48. In support of his arguments that alkaline salts are basic salts that are made under basic conditions, Dr. Davies appears to state that (1) acidic conditions cannot be used to prepare the enantiomers of (-)-omeprazole (Davies Decl. ¶¶ 48, 67) and that (2) acid addition salts of (-)-omeprazole could not exist because they would be inherently unstable. *Id*. I disagree with both propositions.

49. Referring to the DE '455 German reference ("the Kohl reference") (D.I. 111-2, HAN0039827-844), which is the reference alluded to by Dr. Davies in paragraphs 48 and 67, the '504 patent specification describes the preparation of the enantiomers of omeprazole by preparing diastereomers of racemic omeprazole, separating the diastereomers, and hydrolyzing the ester portion off, to obtain the isolated enantiomers. (Col. 1, ll. 26-42.) Both the Kohl reference and the '504 patent specification, describe that the hydrolysis step used to obtain the enantiomers is carried out in concentrated sulfuric acid. In order to avoid degradation, the

acidic solution is neutralized with concentrated sodium hydroxide. While this procedure would be disadvantageous commercially because it is highly exothermic, neither the Kohl reference nor the '504 patent states that the prior art was unsuccessful in preparing optically pure enantiomers of omeprazole as stated by Dr. Davies. (Davies Decl. ¶ 67.)

50. To the contrary, the Kohl reference makes clear that the (+)-enantiomer of omeprazole was obtained -- *under acidic conditions* -- as an amorphous solid product having an optical rotation of $[\alpha]^{23}_{D} = +165^{o}$. (D.I. 111-2 at HAN0039593 (Example 6)). This value is higher than the optical rotation value reported in the '504 patent for (+)-enantiomer of omeprazole formed in Example 13. It is generally well-known that the higher the absolute value of the optical rotation is, the more optically pure the sample is.

51. Both the '504 patent and the Kohl reference make clear that acidic conditions can be used to prepare the enantiomers of omeprazole.

52. In addition, acid salts of the (-)-enantiomer of omeprazole can certainly be prepared and they are not inherently unstable. Dr. Davies concedes that acid salts indeed can be formed: "(-)-omeprazole is 'amphoteric,' which means that it is able to form a salt either under basic conditions by loss of a proton or under acidic conditions by addition of a proton." (Davies Decl., D.I. 133-3, ¶ 38 at p. 13.) In paragraph 39 of his declaration, Dr. Davies illustrates formation of an alkaline salt, and then in paragraph 40, the formation of an acid salt of (-)-omeprazole is depicted. *Id.* at 14. Thus, I disagree with Dr. Davies' statements that those skilled in the art would understand "pharmaceutically acceptable salt" in the '192 patent to refer only to alkaline salts and not to acid addition salts (Davies Decl. ¶¶ 67-68) as plainly incorrect and unsupported.

53. The relevant scientific literature clearly establishes that acid addition salts of omeprazole can be made and are stable. AstraZeneca's U.S. Patent No. 4,337,257 (Ex. 9), issued June 29, 1982, and discloses acid addition salts of omeprazole:

> Depending on the process conditions and the starting materials, the end product is obtained either as the free base or in the acid addition salt, both of which are included within the scope of the invention. Thus, basic, neutral or mixed salts may be obtained as well as hemi, mono, sesqui or polyhydrates. The acid addition salts of the new compounds may in a manner known per se be transformed into free base using basic agents such as alkali or by ion exchange. On the other hand, the free bases obtained may form salts with organic or inorganic acids. In the prepartion of acid addition salts preferably such acids are used which form suitable therapeutically acceptable salts. Such acids include hydrohalogen acids, sulfonic, phosphoric, nitric, and perchloric acids; aliphatic, alicyclic, aromatic, heterocyclic carboxy or sulfonic acids, such as formic, acetic, propionic, succinic, glycolic, lactic, malic, tartaric, citric, ascorbic, maleic, hydroxymaleic, pyruvic, phenylacetic, benzoic, p-aminobenzoic, antranilic, p-hydroxybenzoic, salicylic or p-aminosalicylic acid, embonic, methanesulfonic, ethanesulfonic, hydroxyethanesulfonic, ethylenesulfonic, halogenbenzenesulfonic, toluenesulfonic, naphthylsulfonic or sulfanilic acids; methionine, tryptophane, lysine or arginine.
>
> These or other salts of the new compounds, as e.g. picrates, may serve as purifying agents of the free bases obtained. Salts of the bases may be formed, separated from solution, and then the free base can be recovered from a new salt solution in a purer state. Because of the relationship between the new compounds in free base form and their salts, it will be understood that the corresponding salts are included within the scope of the invention.[14] (Ex. 9; Col. 5, ll. 17-40).

54. Other references clearly establish the existence of acid addition salts of omeprazole. For example, omeprazole hydrochloride is a prior art compound disclosed in U.S. Patent No. 5,066,652 (1991) (Ex. 10). Obviously, if the prior art taught how to make acid salts of omeprazole, acid salts of the enantiomers of omeprazole could be made by the same techniques.

[14] AstraZeneca's U.S. Patent Nos. 4,255,431 and 4,508,905 contain identical disclosure.

55. U.S. Patent 6,255,502 (2001) (Ex. 11) specifically discloses capric acid and lauric acid salts of omeprazole and methods for making those salts.

56. M. Karthikeyan et al.[15] disclose formulation experiments on omeprazole hydrochloride purchased from a commercial source. Dr. Davies unsupported conclusions that persons of ordinary skill in the art would not understand pharmaceutically acceptable salts of (-)-omeprazole to include acid addition salts is squarely contradicted by AstraZeneca's own earlier patents, and other references, showing the preparation of various omeprazole acid salts.

B. Issues Regarding Optical Purity In Both Patents

"(-)-enantiomer of 5-methoxy-2[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole" – '504 patent independent claims 1, 6 and 7 and "optically pure" – dependent claim 2

57. I understand that AstraZeneca stands by its representations to the Court in *AZ v. DRL* action and views the resulting constructions as correct. For the reasons set forth in my Declaration of November 3, 2011 (¶¶ 27-48), I remain of the view that the '504 patent specification and prosecution history do not support adding numerical limitations to any of the '504 or '192 patent claims.

58. I have reviewed Dr. Davies' opinions provided in his November 7, 2011 Declaration Appendix on issues concerning optical purity in both patents. As a general matter, Dr. Davies, as with AstraZeneca's previously articulated claim construction arguments, dismisses the unambiguous express language of the '504 patent -- defining the "optically pure" Na salts of omeprazole as "the (+)-enantiomer of omeprazole Na-salt essentially free of the (-)-enantiomer of omeprazole Na-salt and the (-)-enantiomer essentially free of the (+)-enantiomer, respectively." (Col. 3, ll. 30-35.)

[15] M. Karthikeyan et al., *Formulation and Comparative Studies of Diclofenac With Omeprazole and Diclofenac With Pantoprazole*, 1:1 J. PHARM. & BIOMEDICAL SCIS. 1-4 (2010) (Ex. 12).

59. Instead, Dr. Davies relies essentially solely on the Examples of the '504 patent to read lower numerical limits into the claims, which is improper for the reasons set forth in my earlier Declaration. Dr. Davies fails to explain why the patent "examples" function to narrow and confine the scope of the claims, in violation of the clear language of the patent which states the opposite is true. As I explained in my previous declaration, the '504 specification prefaces the Examples with the following unambiguous statement:

> The invention is ***illustrated*** by the following ***examples*** using ***preferred procedures*** for the preparation of optically pure sodium salts and magnesium salts. '504 patent, col. 6, ll. 26-28 (emphasis added).

60. Dr. Davies considered this language and opined that the use of the term "illustrated" signaled a limiting definition of the optical purity of the claimed compounds based strictly on the examples that followed this statement. (Davies Tr. 209-210.) I disagree that ***examples illustrating*** an invention using only ***preferred procedures*** for preparation provide limiting definitions of claimed features.

61. Dr. Davies' improper methodology for importing limitations of the Examples into the claims begins with his explanation of the prior art 1990 Erlandsson publication, which is discussed in the background section of the '504 patent (col. 1, ll. 27-29) (Davies Decl. Appendix ¶¶ 7-9). According to Dr. Davies, the "patent provides (-)-omeprazole at an optical purity not provided by prior art methods." (Davies Decl. Appendix ¶ 6.) Because the Erlandsson reference disclosure of (-)-omeprazole in an optical purity of 95.6% (91.2% e.e.) is prior art, Dr. Davies concludes that the '504 patent claims cannot be construed to include compounds having optical purity at the levels disclosed in the Erlandsson reference, even though (1) the express definition of optically pure in the '504 patent is not defined by a numerical value; and (2) none of the claims contained a numerical value as a limitation on

optical purity. I disagree with Dr. Davies' methodology as well as his reading of the Erlandsson reference.

62. First, there is no dispute that the Erlandsson reference is directed to the separation of racemic omeprazole into its enantiomers, which are obtained in neutral form, *i.e.*, as free bases and not as salts as recited in the asserted claims 1-7 and 10 of the '504 patent. Distinguishing the claimed salts of (-)-omeprazole from the prior art disclosures of the neutral forms, the '504 patent states:

> There is no example in the known prior art *of any isolated or characterized salt of optically pure omeprazole*, i.e. of single enantiomers of omeprazole or of any isolated or characterized salt of any optically pure omeprazole analogue. (Col. 1, ll. 43-47.)

63. This statement makes clear the patentees' view that that the prior art did not disclose any salt of optically pure omeprazole whether as a single enantiomer or as an analog thereof. Because the asserted salt claims of the '504 patent do not encompass the neutral form of omeprazole's enantiomers, there is no connection with or reason to limit the optical purity of the claimed salts based on a prior art disclosure of neutral forms of the single enantiomers. A person skilled in the art would simply not understand that the optical purity of the claimed salts is in any way limited or defined by the optical purity of the prior art enantiomers in neutral form.

64. Even if the Erlandsson reference disclosure of (-)-omeprazole neutral form having an optical purity of 91.2% e.e. were relevant to the interpretation of the '504 patent claims (which it is not), Dr. Davies provides no reason why the lower limit of optical purity of the claimed ***salts*** of (-)-omeprazole is 94% e.e., or why salts of (-)-omeprazole having an optical purity of, *e.g.*, between 91.2% e.e. and 94% e.e. would be outside the scope of the claims lacking any purity limitation at all. In fact, the only disclosure of 94% e.e. is in Example 12, which is the

neutral form of (-)-omeprazole and not its salt. The '504 patent does not have any disclosure whatsoever linking the optical purity of any salt form to 94% e.e.

65. Dr. Davies' methodology of (1) selecting as a starting point the prior art disclosure of the neutral form (-)-omeprazole as a basis for establishing a lower limit on the optical purity of the claimed salts, (2) arbitrarily importing the 94% optical purity value of the neutral form from Example 12 into the salt claims, and (3) failing to explain how or why compounds having an optical purity between 91.8% e.e. and 94% e.e. would not be included within the scope of the claims is flawed and unsupported.

66. In addition, Dr. Davies ignores the Erlandsson reference's teaching of (+)-omeprazole, obtained at an enantiomeric purity of 82% (64% e.e.) (D.I. 133-5 at 317), and fails to explain why (even using his own flawed methodology) he did not consider the optical purity of the (+)-enantiomer in determining the lower limit of the '504 patent claims. I believe it is inconsistent for Dr. Davies to have repeatedly relied on Examples 1, 3, 4 and 7 of the '504 patent (all directed to salts of *(+)-omeprazole*) to support his views about the interpretation of the claims, but to have wholly disregarded the prior art teachings of (+)-omeprazole in the Erlandsson reference in arbitrarily concluding the lower limit of the optical purity of the salts of claim 1 is 94% e.e.

67. Further, as I stated in my initial Declaration and explained at my deposition, the optical purities of the *neutral forms* of (-)-omeprazole in Example 12 and in the Erlandsson reference neither support nor limit the optical purities of the alkaline *salts* of (-)-omeprazole in the claims. (Atwood Decl. ¶¶ 34-35; Atwood Tr. 190; 194-97; 222-24 (Ex. 2).) The enantiomers of omeprazole in non-salt or neutral form are not part of the invention of the '512 application as filed, because they were admittedly known in the prior art. There is no basis to

limit the optical purity of a claimed (-)-omeprazole salt based on the prior art disclosure of the optical purity of a single enantiomer *in neutral form*.

68. Dr. Davies urges that "optically pure" of Claim 2 means at least 98% e.e. I disagree with his flawed methodology of limiting "optically pure" in the claims based on measured values for compounds reported in the Examples. Even using his methodology, none of the examples support a 98% e.e. limitation. The closest value in the examples provided by the Examples for a (-)-omeprazole salt is 98.4% in Example 6, and Prof. Davies has not explained how the claims could encompass compounds having an optical purity between 98.0 - 98.4% e.e., particularly given his views about the optical purity of the neutral form in Example 12. The only example of a salt form at 98% e.e. is for a (+)-enantiomer (Example 3).

69. Dr. Davies' inconsistent and selective reliance on the teachings of the Erlandsson reference and the '504 patent Examples further supports my conclusion that there is nothing in the '504 patent documents which support adding any numerical limitations into the '504 claims, let alone the 94% -98% e.e. values for ***salts*** according to the patent.

70. With respect to the '192 patent claims which encompass both the neutral form of the (-)-enantiomer and pharmaceutically acceptable salts thereof, Dr. Davies asserts that the '504 patent specification can be used to assign a lower optical purity limit of 98% e.e. In fact, there is no disclosure in the '504 patent of a neutral form of a ***(-)***-enantiomer having an optical purity of 98%. The only example of a free enantiomer reported as 98% e.e. is Example 13 directed to a ***(+)***-enantiomer. And as pointed out above, there is no disclosure in the '504 patent of a (-) salt having an optical purity of 98% e.e. Thus, even under the improper methodology of limiting the claims to numerical values found only in illustrative working examples – based on

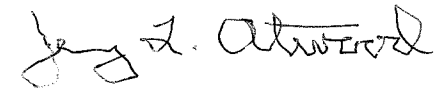
an incorrect baseline from the Erlandsson disclosure (*i.e.*, selecting only the 91.2% value while ignoring the 64% e.e. value) – the examples do not match the conclusions drawn.

71. In summary, it is undisputed that:

- The '504 patent discloses no salt, much less a (-)-omeprazole salt, having an optical purity of 94% e.e.; therefore there is no basis for limiting Claim 1 to 94% e.e.
- With respect to Claim 2 of the '504 patent, there is no example of a (-)-omeprazole salt having an optical purity of 98% e.e.; therefore, there is no basis for limiting Claim 2 to 98% e.e.
- With respect to the claims of the '192 patent, there is no example of a neutral (-)-enantiomer or a (-)-omeprazole salt having an optical purity of 98% e.e.; therefore there is no basis for limiting the '192 claims to 98% e.e.
- Because AstraZeneca's and Dr. Davies' methodology relies on reported values for non-claimed compounds in both the '504 and '192 patents, their baseline for the lower limit of the optical purity (which relies only on the (-)- enantiomer (91.2% e.e.) and not the (+)-enantiomer (64% e.e.)) is incorrect and therefore invalid.

I declare under penalty of perjury that the foregoing is true and correct.

Dated: January 6, 2012



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